

Progressive diffuse muscular pain and stiffness of the torso

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PART A

A 65-year-old male patient presented at the emergency department with progressive diffuse muscular pain and stiffness lasting for two weeks. Symptoms presented initially in the shoulders, extending within four days to the back. His medical history included gout and hypercholesterolaemia under treatment for one month and three years respectively. On admission, physical exam-

ination revealed severe torso muscle weakness and tenderness, mostly in the back. The patient was totally unable to raise the body from supine position. Laboratory studies showed elevated creatine kinase (2150 mg/dL) and creatinine plasma levels (1.68 mg/dL). An MRI examination of the thorax and abdomen was performed (Figs. 1, 2).

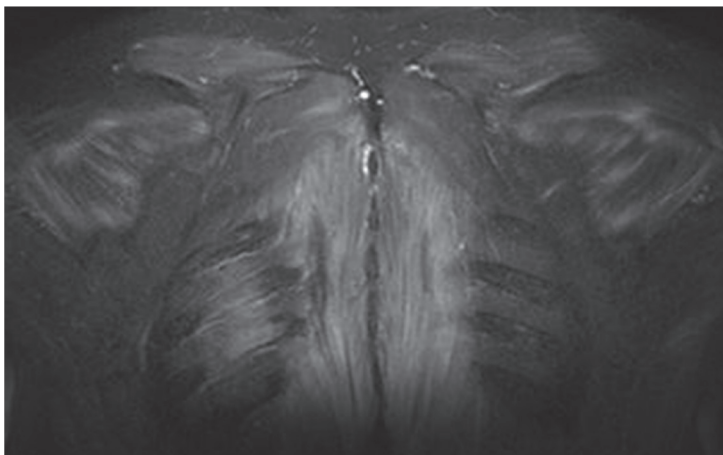


Fig 1. Coronal STIR MR image of the upper back.



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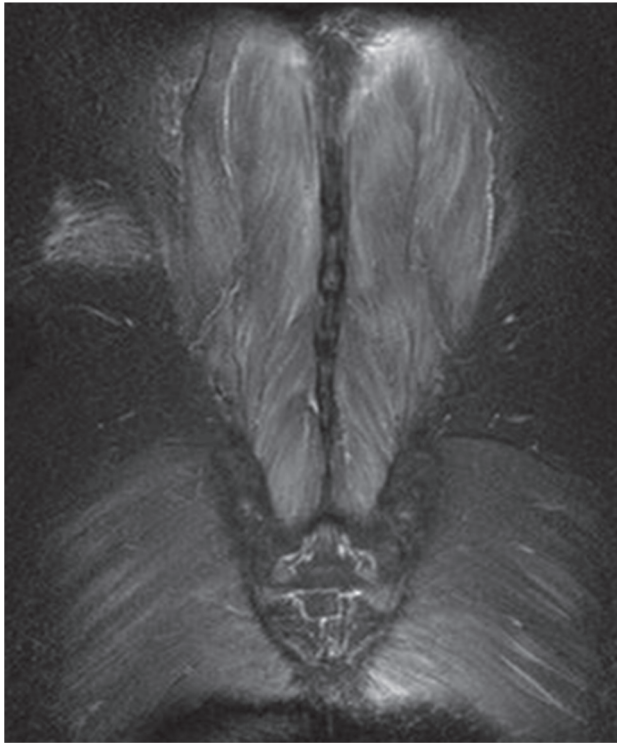


Fig 2. Coronal STIR MR image of the lower back.



Fig 3. Coronal STIR MR image at the level of the hip joints.

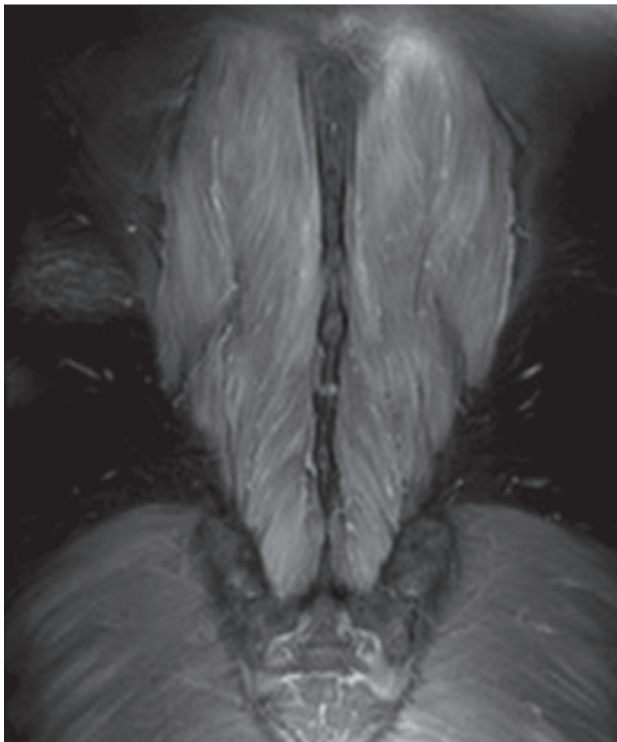


Fig. 4. Coronal fat suppressed contrast enhanced T1-w MR image of the lower back.

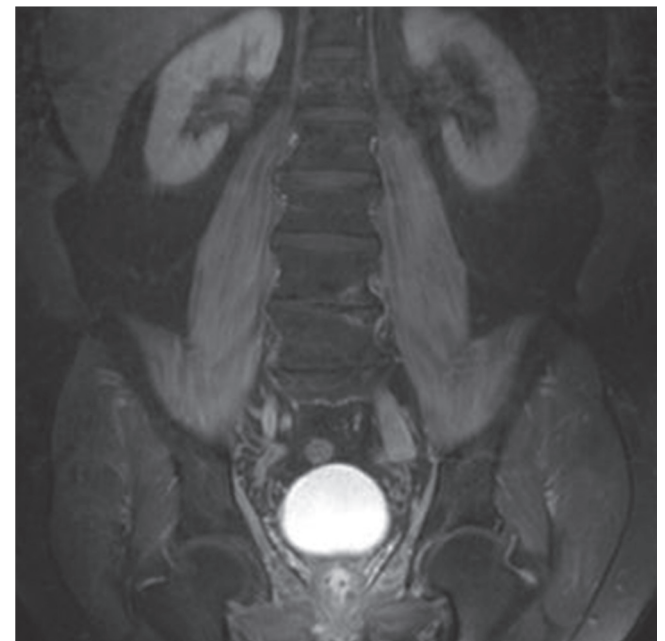


Fig. 5. Coronal fat suppressed contrast enhanced T1-w MR image at the level of the hip joints.

PART B

Diagnosis: Acute rhabdomyolysis due to drug induced myopathy

A drug induced, or toxic, myopathy is defined as the acute or subacute manifestation of muscle related signs and symptoms, such as myalgia, fatigue and myoglobinuria or serum creatine kinase (sCK) elevation, associated with administration of a drug, in the absence of previous muscle disease [1]. Rhabdomyolysis is an acute necrotising myopathy characterised by severe pain, muscle weakness and swelling and elevated sCK, at least 10 times the upper normal limit. It is associated with myoglobinuria, which can lead to acute renal failure and death. The diagnosis is usually supported by marked improvement of clinical and biochemical signs after discontinuation of the suspected agent. Elevated sCK concentration is indicative of muscle disease but lacks specificity in its diagnosis and characterisation. As neurophysiological studies are of limited value in muscular disorders, muscle biopsy is often necessary to document the evidence of myotoxicity and eliminate other causes of weakness [2]. In our University Hospital, the diagnostic approach includes MRI, targeting the painful sites, in order to locate the most suitable mus-

cle group for image-guided or blind biopsy. MRI in our patient showed extensive muscle involvement in the torso demonstrating symmetric oedema and swelling on STIR sequences and homogeneous enhancement of the muscles following paramagnetic contrast medium administration (Figs. 1-5).

In adults, myopathies are disorders with a wide differential diagnosis, including inflammation associated with connective tissue disorders, inclusion body myositis, endocrinopathies, particularly those related to corticosteroid excess, infection and metabolic disturbances [3]. A variety of drugs used for the treatment of common diseases can lead to toxic myopathy. These include cholesterol lowering agents, drugs altering their metabolism, immunosuppressive agents, antinucleoside analogues, as well as dietary and recreational products [1].

HMG-CoA reductase inhibitors, known as statins, are commonly used as cholesterol lowering pharmaceuticals and remain among the most well recognised myotoxic agents [4]. Muscle pain is reported by up to 10% of patients receiving statins, with rhabdomyolysis being a very rare complication [5]. However, due to the wide use of these

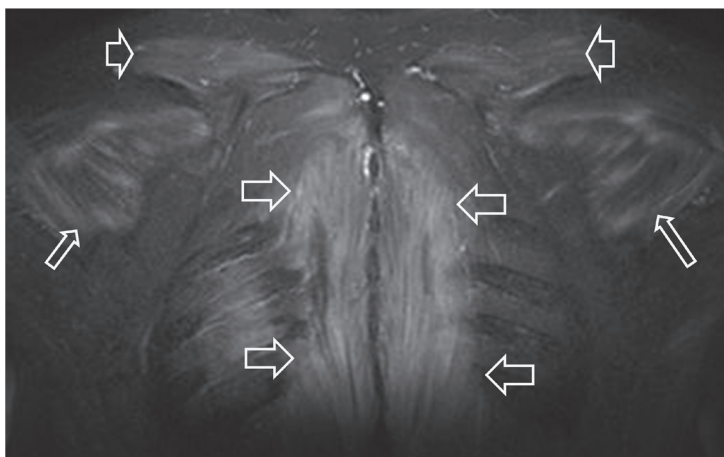


Fig 1. Coronal STIR MR image of the upper back showing bilateral muscle oedema within trapezius (short open arrows), infraspinatus and teres minor (thin open arrows) and semispinalis cervicis and capitis muscles (open arrows).



KEY WORDS

Rhabdomyolysis/chemically induced; MR imaging/diagnosis; Statins; Colchicine; Muscular Diseases

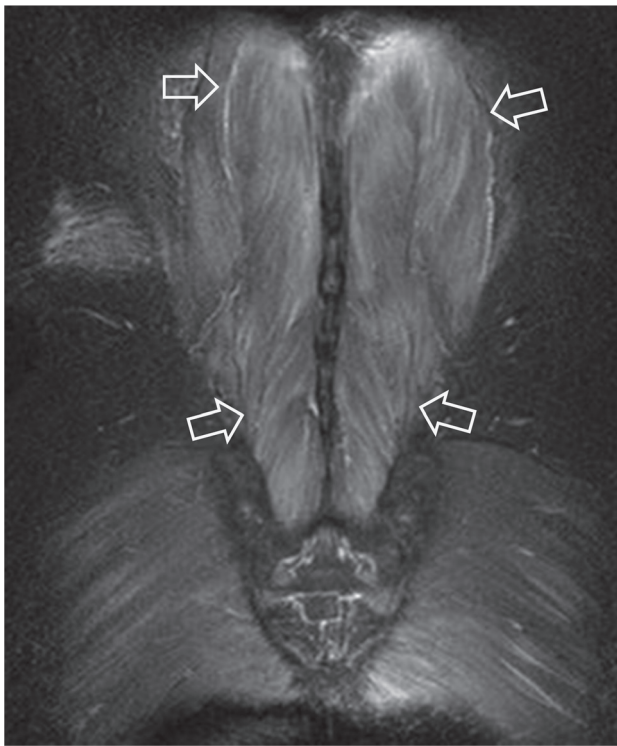


Fig. 2. Coronal STIR MR image of the lower back showing bilateral muscle oedema within longissimus thoracis, quadratus lumborum and multifidus muscles (open arrows).



Fig. 3. Coronal STIR MR image at the level of the hip joints showing symmetrical muscle oedema within psoas (open arrows) and quadratus lumborum muscles (short open arrows).



Fig. 4. Coronal fat suppressed contrast enhanced T1-w MR image of the lower back showing diffuse and symmetric enhancement of longissimus thoracis, quadratus lumborum and multifidus muscles (open arrows).

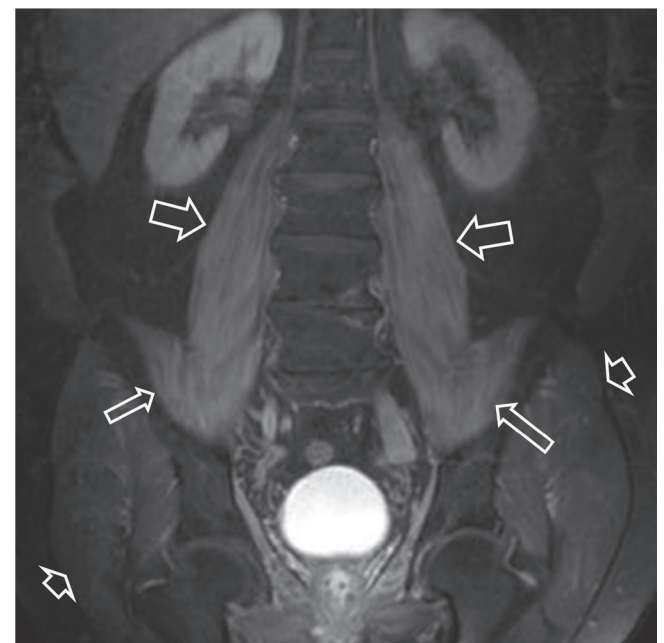


Fig. 5. Coronal fat suppressed contrast enhanced T1-w MR image at the level of the hip joints, showing diffuse and symmetric enhancement of psoas (open arrows) and quadratus lumborum muscle (long open arrows). Note for comparison the normal MRI signal of the gluteal muscles (short open arrows).

agents, a large number of affected individuals in clinical practice is expected. Patients tend to report intermittent muscle pain in the thigh and calf area and a quarter present with generalised myalgia. There is no consensus on the temporal relation between therapy and symptom onset, which can vary from weeks to several years.

The exact mechanisms underlying statin myopathy are not completely understood. Among others, membrane destabilisation due to decreased cholesterol synthesis, coenzyme Q10 depletion and mitochondrial dysfunction have been proposed. Several risk factors have been identified, including complex medical conditions and combinations of several medications, advanced age, frailty and female sex. Increased doses of statins and concomitant drugs, such as those metabolised by the cytochrome P450 3A4 isoenzyme, are well documented risk factors. Several DNA polymorphisms have inconsistently been associated with statin myopathy in the past, with the most notable being in the SLC01B1 gene.

In the majority of such cases, patients recover spontaneously after the cessation of statin treatment. If rhabdomyolysis is present, urine alkalinisation, aggressive fluid administration and rarely short-term dialysis is required. In the case of autoimmune necrotising myopathy however, a recently recognised entity, statins trigger an autoimmune response against muscle cells in susceptible patients, which needs to be controlled with immunosuppressive therapy. Patients present with symmetric proximal weakness, persistently elevated sCK levels (often >2000 IU/L) and prominent muscle-cell necrosis with cellular infiltrates on biopsy. In such patients a positive test for anti-HMG-CoA reductase autoantibodies strongly supports the diagnosis [6].

Colchicine is used today primarily for the treatment of gout and, in a lesser extent, of other disorders such as pulmonary fibrosis, pericarditis, primary cirrhosis, familial Mediterranean fever and Adamantiades-Bechet's disease. Colchicine-induced myopathy is rare and is often manifested after a change of the underlying disease state or an increase of dosage. Patients present with proximal muscle weakness, distal areflexia and mild sensory changes associated with characteristic electromyographic findings [7]. Colchicine acts by preventing the polymerisation of tubulin dimers of the microtubules, inhibiting cell division, leukocyte chemotaxis,

mast cell histamine release and collagen synthesis. The drug directly induces pathologic alterations in skeletal muscle cells and large myelinated axons, causing myopathy which usually clinically predominates over neuropathy [7]. Impaired renal function represents a risk factor for toxicity and it is recommended that doses over 0.6 mg twice/day should not be administered to patients with creatinine clearance under 50 ml/min. It is also worth noting that colchicine is not removed by dialysis [7].

Colchicine-triggered myopathy in patients receiving statins has been suggested in case reports in the literature. Colchicine lies among the most frequently co-prescribed drugs with statins, with a potential interaction [8]. A proposed mechanism suggests that as both colchicine and the majority of available statins are metabolised by CYP3A4 isoenzyme in the liver, concomitant administration may lead to increased serum concentrations and risk for side effects [9]. Acute renal failure after such combined drug administration may be reversible [10].

Our patient had no symptoms under treatment with statins. Thus colchicine, which was introduced a few weeks before the onset of symptoms, might have triggered or promoted the development of myopathy and rhabdomyolysis. As the history was quite supportive and MRI and biochemical findings were highly indicative, the patient was treated without biopsy with drug cessation, steroid and intravenous fluid administration. The patient was discharged nine days after admission with the estimated glomerular filtration rate increasing from 41 to 55 mL/min/1.73 m².

In conclusion, both statin and colchicine use are associated with myopathy demonstrated with muscle pain and weakness and rarely rhabdomyolysis. If concomitant administration increases risk, it remains to be proven. In clinical practice, in such patients it is worth acquiring a baseline sCK level and querying patients for symptoms of myotoxicity at every visit. Caution should be exercised when prescribing statins and colchicine, especially for patients in the previously recognised high-risk group. MRI has an important role in aiding the diagnosis and assessing the extent of involvement. **R**

Conflict of interest

The authors declared no conflicts of interest.

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